ClinicalEvidence

Chronic fatigue syndrome

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ABSTRACT

INTRODUCTION: Chronic fatigue syndrome (CFS) affects between 0.006% and 3% of the population depending on the criteria of definition used, with women being at higher risk than men. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for chronic fatigue syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2007 (BMJ Clinical evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 45 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antidepressants, cognitive behavioural therapy (CBT), corticosteroids, dietary supplements, evening primrose oil, galantamine, graded exercise therapy, homeopathy, immunotherapy, intramuscular magnesium, oral nicotinamide adenine dinucleotide, and prolonged rest.

QUESTIONS

INTERVENTIONS

Key points

- Chronic fatigue syndrome (CFS) is characterised by severe, disabling fatigue, and other symptoms including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches.

  CFS affects between 0.006% and 3% of the population depending on the criteria used, with women being at higher risk than men.

- Graded exercise therapy has been shown to effectively improve measures of fatigue and physical functioning.

  Educational interventions with encouragement of graded exercise (treatment sessions, telephone follow-ups, and an educational package explaining symptoms and encouraging home-based exercise) improve symptoms more effectively than written information alone.

- CBT is also effective in treating chronic fatigue syndrome.

  CBT may also be beneficial when administered by therapists with no specific experience of chronic fatigue syndrome, but who are adequately supervised.

  In adolescents, CBT can reduce fatigue severity and improve school attendance compared with no treatment.

- We don't know how effective antidepressants, corticosteroids, and intramuscular magnesium are in treating chronic fatigue syndrome.

  Antidepressants should be considered in people with affective disorders, and tricyclics in particular have potential therapeutic value because of their analgesic properties.

- Interventions such as dietary supplements, evening primrose oil, oral nicotinamide adenine dinucleotide, homeopathy, and prolonged rest have not been studied in enough detail for us to draw conclusions on their efficacy.

- A large study has found that galantamine is no better than placebo at improving symptoms of chronic fatigue syndrome.

- Although there is some evidence that immunotherapy can improve symptoms compared with placebo, it is associated with considerable adverse effects, and should therefore probably not be offered as a treatment for chronic fatigue.

Chronic fatigue syndrome

DEFINITION

Chronic fatigue syndrome (CFS) is characterised by severe, disabling fatigue, and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches. Two widely used definitions of CFS, from the US Centers for Disease Control and Prevention (CDC) (current criteria issued in 1994, which superseded the CDC criteria issued in 1988) [1] and from Oxford, UK, [2] were developed as operational criteria for research (see table 1, p 18). The principal difference between these definitions is the number and severity of symptoms, other than fatigue, that must be present. A third operational definition, the Australian criteria, is similar to the CDC diagnostic criteria, and has also been used in treatment trials. [3] The 1994 CDC criteria were recently reviewed with the aim of improving case ascertainment for research. [4] The exclusion criteria were clarified, and the use of specific instruments for the assessment of symptoms was recommended. [4]

INCIDENCE/ PREVALENCE

Community- and primary-care-based studies have reported the prevalence of CFS to be from 0.007% to 2.8% in the general adult population, and from 0.006% to 3.0% in primary care depending on the criteria used. [5]

AETIOLOGY/ RISK FACTORS

Despite considerable research effort and several hypotheses, the cause of CFS remains poorly understood. Endocrine and immunological abnormalities have been found in many people, although it is unclear whether these changes are causal, or are part of the course of the syndrome. Certain infectious illnesses, such as Epstein–Barr virus, Q fever, and viral meningitis, are associated with a greater risk of developing CFS, but many people have no evidence of viral infection, and there is no evidence of persistent infection. [6] People with prior psychiatric disorders are more likely to report with CFS later in life (OR 2.7, 95% CI 1.3 to 5.6). [7] Women are at higher risk than men (RR 1.3–1.7, depending on diagnostic criteria used; confidence intervals not reported). [8] Population surveys in the USA have found that white people have a lower risk of CFS compared with Latin Americans, African-Americans, and Native Americans. [9] [10]

PROGNOSIS

Studies have focused on people attending specialist clinics. A systematic review of studies of prognosis (search date 1996) found that children with CFS had better outcomes than adults: 54–94% of children showed definite improvement in symptoms (after up to 6 years' follow-up), whereas 20–50% of adults showed some improvement in the medium term (12–39 months) and only 6% returned to premorbid levels of functioning. [11] Despite the considerable burden of morbidity associated with CFS, we found no evidence of increased mortality. The systematic review found that a longer duration of illness, fatigue severity, comorbid depression and anxiety, and a physical attribution for CFS are factors associated with a poorer prognosis. [11] A more recent review found a median full recovery rate of 5% (range 0–31%), and the median proportion of patients who improved during follow-up to be 39.5% (range 8–63%). Good outcome was associated with less fatigue severity at baseline, a sense of control over symptoms, and not attributing the illness to a physical cause. [12]

AIMS OF INTERVENTION

To reduce levels of fatigue and associated symptoms, to increase levels of activity, and to improve quality of life.

OUTCOMES

Severity of symptoms and their effects on physical function and quality of life. There are several different instruments used to measure these outcomes, including: the medical outcomes survey short form general health survey (SF-36, [13] a rating scale measuring quality of life, including limitation of physical functioning caused by ill health [score range 0–100, where 0 = limited in all activities and 100 = able to carry out vigorous activities], pain, energy levels, and mood); the Karnofsky scale, [14] a modified questionnaire originally developed for the rating of quality of life in people having chemotherapy for malignancy (where 0 = death and 100 = no evidence of disease); the Beck Depression Inventory, [15] a checklist for quantifying depressive symptoms (score range 0–63, where a score of 20 or more is usually considered clinically significant depression); the Hospital Anxiety and Depression scale (HADS, [16] consists of 2 subscales, each with score range 0–21, where a score of 11 or more is considered clinically significant); the Sickness Impact Profile, [17] a measure of the influence of symptoms on social and physical functioning; the Chalder Fatigue Scale, [18] a rating scale measuring subjective fatigue (score range 0–11, where scores 4 or more = excessive fatigue); the Abbreviated Fatigue Questionnaire, [19] a rating scale of subjective bodily fatigue (score range 4–28, where a lower score indicates a higher degree of fatigue); the Clinical Global Impression scale, [20] a validated measure of overall change compared with baseline at study onset (7 possible scores from “very much worse” [score 7] to “very much better” [score 1]); the Checklist Individual Strength fatigue subscale (score range 8 [no fatigue at all] to 56 [maximally fatigued]); [21] the Nottingham Health Profile, [22] with questions in six self-report categories: energy, pain perception, sleep patterns, sense of social isolation, emotional reactions, and physical mobility (maximum weighted score 100 [all listed complaints present], and minimum 0 [none of listed complaints present]); the Multidimensional Fatigue Inventory (MFI), [23] with five subscales:

general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation (each with a score range of 4–20, higher scores indicate higher degree of fatigue); and self-reported severity of symptoms and levels of activity.

METHODS

BMJ Clinical Evidence search and appraisal September 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2007, Embase 1980 to September 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 3. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by two information specialists. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded for drug interventions, and non-blinded or open for non-drug interventions, and containing more than 20 people, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 19).

QUESTION What are the effects of treatments for chronic fatigue syndrome?

OPTION CBT

Overall improvement

Compared with control interventions CBT may be more effective at increasing complete recovery at 5 years (low-quality evidence).

Quality of life

Compared with control interventions We don't know whether CBT is more effective than usual care at improving quality of life (very low-quality evidence).

Fatigue

Compared with control interventions CBT may be more effective at improving fatigue (very low-quality evidence).

Physical functioning

Compared with control interventions We dont know whether CBT is more effective at improving physical functioning (very low-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits:

CBT versus control interventions:

We found one systematic review (search date 2005), [24] which did not perform a meta-analysis or report quantified results from each study, and one subsequent RCT. [25] The review identified five RCTs that met the reviewers' inclusion criteria (all participants fulfilled accepted diagnostic criteria for chronic fatigue syndrome [CFS], and the trials used adequate randomisation and controls). [26] [27] [28] [29] [30] The first RCT (90 people with CFS, Australian criteria, similar to Centers for Disease Control and Prevention [CDC] criteria) identified by the review evaluated CBT and immunological therapy (dialysable leucocyte extract, DLE) using a factorial design. [26] The four treatment arms were: CBT plus DLE; CBT plus placebo (saline); usual care plus DLE; and usual care plus placebo (saline). CBT was given every 2 weeks for six sessions of 30–60 minutes each, and people were encouraged to exercise at home, and to feel less helpless. The trial found no significant difference in quality-of-life measures (Karnofsky scale and symptom report on a visual analogue scale) between pooled CBT groups and pooled usual care groups (no data presented; P value not reported). The second RCT (60 people with CFS, Oxford criteria) identified by the review compared CBT versus usual general-practice care in people attending a secondary-care centre. [27] The active treatment consisted of a cognitive behavioural assessment, followed by 16 weekly sessions of behavioural experiments, problem-solving activity, and re-evaluation of thoughts and beliefs that inhibited a return to normal functioning. It found that CBT significantly improved quality of life (Karnofsky scale) at 12 months compared with usual care (final score greater than 80: 22/30 [73%] with CBT *v* 8/30 [27%] with placebo; RR 2.75, 95% CI 1.54 to 5.32; NNT 3, 95% CI 2 to 5). The third RCT identified by the review (278 people with CFS, CDC criteria) compared CBT, guided-support groups, or no intervention. [29] The CBT consisted of 16 sessions over 8 months administered by 13 therapists with no previous experience of treating CFS. The guided-support groups

were similar to CBT in terms of treatment schedule, with people receiving non-directive support from a social worker. At 8 months' follow-up, the RCT found that more people in the CBT group met the criteria for clinical improvement in fatigue severity (Checklist Individual Strength [CIS-fatigue]) and self-reported improvement in fatigue compared with the guided-support and no-intervention groups (improved fatigue severity: 27/83 [33%] with CBT *v* 10/80 [13%] with guided support, RR 2.6, 95% CI 1.3 to 5.0; 27/83 [33%] with CBT *v* 8/62 [13%] with no intervention, RR 2.5, 95% CI 1.2 to 5.2; self-reported improvement: 42/74 [57%] with CBT *v* 12/71 [17%] with guided support, RR 3.4, 95% CI 1.9 to 5.8; 42/74 [57%] with CBT *v* 23/78 [30%] with no intervention, RR 1.9, 95% CI 1.3 to 2.9; analysis not by intention to treat, see comment below). The fourth RCT compared CBT versus no intervention in adolescents. [30] CBT consisted of 10 sessions over 5 months. The RCT found that CBT significantly reduced fatigue severity (CIS-fatigue) and functional impairment (SF-36) at 5 months compared with no treatment (69 people, age 10–17 years, CDC criteria; change in CIS-fatigue score: –22.3 with CBT *v* –7.6 with no intervention, difference 14.5, 95% CI 7.4 to 21.6; change in SF-36 score: 27.3 with CBT *v* 10.0 with no treatment, difference 17.3, 95% CI 6.2 to 28.4). The RCT also found that CBT significantly improved school attendance (% change in school attendance: 28% with CBT *v* 10% with no treatment; difference 18%, 95% CI 0.8% to 35.5%). The fifth RCT (60 people with CFS, CDC diagnostic criteria in people attending a secondary-care centre) identified by the review compared CBT versus relaxation therapy. [28] It found that CBT significantly improved physical functioning compared with relaxation therapy (improvement based on predefined absolute or relative increases in the SF-36 score: 19/30 [63%] with CBT *v* 5/30 [17%] with relaxation; RR 3.70, 95% CI 2.37 to 6.31; NNT 3, 95% CI 1 to 7). Improvement continued over 6–12 months' follow-up. CBT was given in 13 weekly sessions. A 5-year follow-up study of 53 (88%) of the original participants found that more people rated themselves as “much improved” or “very much improved” with CBT compared with relaxation therapy (17/25 [68%] with CBT *v* 10/28 [36%] with relaxation therapy; RR 1.9, 95% CI 1.1 to 3.4; NNT 4, 95% CI 2 to 19). [31] More people treated with CBT met the authors' criteria for complete recovery at 5 years, but the difference was not significant (17/31 [55%] with CBT *v* 7/22 [32%] with relaxation therapy; RR 1.7, 95% CI 0.9 to 3.4).The subsequent RCT (153 people with CFS, CDC criteria, 3-arm trial) compared three interventions: group CBT, usual care, and education and support (EAS). [25] CBT (52 people) consisted of 8 sessions over 16 weeks administered by experienced therapists. The education and support group (50 people) met the same therapists as those with CBT, in the same setting, for the same duration, and were taught a different relaxation exercise each week. The usual-care group (51 people) was managed in primary care and only attended the hospital for assessment at baseline and at 6 and 12 months. Treatment effects at 6 and 12 months were pooled for analysis. The RCT found that CBT significantly improved mental health as assessed by SF-36 compared with usual care, but not compared with education and support (CBT *v* usual care: 4.35, 95% CI 0.72 to 7.97, P = 0.019; CBT *v* education and support: 3.16, 95% CI –0.05 to +6.38, P = 0.5; P among groups = 0.04). There was no significant difference among groups in physical health assessed by SF-36 (CBT *v* usual care: –1.63, 95% CI –4.05 to +0.78, P value not reported, reported as not significant; CBT *v* education and support: –4.0, 95% CI –2.86 to +2.06, P value not reported, reported as not significant; P among groups = 0.36). The RCT also found that CBT significantly decreased physical fatigue (Chalder Fatigue Score) compared with both usual care and education and support (CBT *v* usual care: –2.61, 95% CI –4.92 to –0.30, P = 0.03; CBT *v* education and support: –3.16, 95% CI –5.59 to –0.74, P = 0.011; P among groups = 0.03). The RCT found only a borderline significant difference in Hospital Anxiety and Depression score (HADS) in anxiety, between CBT and usual care, but found no significant difference between CBT and education and support in anxiety, or between CBT and the other groups in depression (HADS anxiety: CBT *v* usual care: –1.27, 95% CI –2.52 to –0.02, P = 0.045; CBT *v* education and support: –0.51, 95% CI –1.70 to +0.68, P value not reported, reported as not significant; P among groups = 0.13; HADS depression: CBT *v* usual care: –0.56, 95% CI –1.69 to 0.58, P value not reported, reported as not significant; CBT v education and support: –0.13, 95% CI –1.13 to +0.87, P value not reported, reported as not significant). [25] No adjustments were made for the multiple number of statistical tests carried out.

Harms: The RCTs gave no information on adverse effects. [25] [26] [27] [28] [29] [30]

Comment: The multi-centre RCT [29] had a high withdrawal rate (25% after 8 months), especially in the CBT and guided-support groups. Although the presented confidence intervals are not adjusted for multiple comparisons, the results would remain significant after any reasonable adjustment. The authors commented that the results were similar after intention-to-treat analysis, but these results were not presented. [29] A randomised trial comparing CBT and non-directive counselling found that both interventions were of benefit in the management of people who consulted their family doctor because of fatigue symptoms. [32] In this study, 28% of the sample conformed to CDC criteria for CFS.

Clinical guide:
There is moderate evidence of benefit for CBT in CFS. The effectiveness of CBT for CFS outside of specialist settings has been questioned. The results of the multi-centre RCT [29] suggest that CBT may be effective when administered by less-experienced therapists with adequate supervision.

OPTION GRADED EXERCISE THERAPY

Overall improvement
Compared with control interventions Graded exercise therapy may lead to greater overall improvement in symptoms (low-quality evidence).

Fatigue
Compared with control intervention Graded aerobic exercise programmes may be more effective at improving measures of fatigue compared with flexibility training and relaxation training or general advice (low-quality evidence).

Compared with written information An educational package to encourage graded exercise is more effective at improving measures of physical functioning and fatigue at 1 year compared with written information alone (moderate-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits:

We found two systematic reviews (search date 2004, [33] search date 2005 [24]). The first systematic review included the results of an unpublished RCT in its meta-analyses, and so we have reported the results of the three published RCTs identified by the review individually. The second systematic review did not perform a meta-analysis or report quantified results from each study, and identified one additional RCT not included in the first systematic review. [34]

Graded exercise therapy versus control interventions:
The first systematic review identified three RCTs [35] [36] [37] and the second systematic review found one additional RCT. [34] The first RCT identified by the first review (66 people with chronic fatigue syndrome [CFS], Oxford criteria) compared graded aerobic exercise (active intervention) versus flexibility and relaxation training (control intervention) over 12 weeks. [35] All participants had individual weekly sessions supervised by an exercise physiologist. People in the aerobic-exercise group built up their level of activity to 30 minutes of exercise a day (walking, cycling, swimming up to a maximum oxygen consumption of 60% of V_{O2} max). People in the flexibility and relaxation training group were taught stretching and relaxation techniques (maximum 30 minutes daily, 5 days/week) and were specifically told to avoid any extra physical activities. The RCT found that graded aerobic exercise significantly increased reports of feeling “much better” or “very much better” compared with the control intervention (Clinical Global Impression Scale: 52% with exercise *v* 27% with control; P = 0.04). It also found that graded aerobic exercise significantly decreased physical fatigue and improved physical functioning compared with control (mean change in Chalder Fatigue Score: –8.4 with exercise *v* –3.1 with control, P = 0.004; mean change in SF-36 physical function score: 20.5 with exercise *v* 8.0 with control; P = 0.01). The second RCT identified by the first review (136 people with CFS, Oxford criteria) compared four interventions: graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine over 24 weeks. [36] The graded-exercise groups were given specific advice to do preferred aerobic exercise (such as walking, jogging, swimming, or cycling) for 20 minutes three times a week up to an energy expenditure of 75% of V_{O2} max. People in the general-advice groups were not given any specific advice on frequency, intensity, or duration of aerobic activity. The RCT found that graded exercise with or without fluoxetine significantly reduced fatigue at 26 weeks compared with general advice with or without fluoxetine (Chalder fatigue score less than 4: 12/67 [18%] with graded exercise *v* 4/69 [6%] with general advice; RR 3.10, 95% CI 1.05 to 9.10; NNT 9, 95% CI 5 to 91). The third RCT identified by the first review (61 people with CFS, Centers for Disease Control and Prevention [CDC] criteria) compared graded aerobic exercise versus relaxation and flexibility training over 12 weeks. [37] Graded activity consisted of aerobic exercise (walking, swimming, or cycling) for up to 15 minutes every second day. Intensity of activity was determined by mean heart rate during exercise. If there was a worsening of symptoms, the next exercise session was shortened or cancelled, and subsequent sessions reduced to a length considered by the participant to be manageable. People in the relaxation and flexibility group listened to a relaxation tape and performed stretching exercises every second day. The RCT found that graded aerobic exercise significantly improved mental fatigue (measured using the 14-item version of the Chalder scale; 6 items for mental fatigue [range 0–6] and 8 items for physical fatigue [range 0–8]; pre- and post-treatment scores were calculated) compared with relaxation and flexibility after 12 weeks (mean change in Chalder fatigue score: 1.8 with exercise *v* 0.8 with control; P = 0.02). However, it found no significant difference in physical fatigue (mean change in physical fatigue score: 3.5 with exercise *v* 1.8 control; P = 0.07). [37] It found no significant difference between the groups in self-reported improvement or anxiety symptoms (Clinical Global Impression Scale: 29/32 [91%]

with exercise *v* 22/29 [76%] with control, P = 0.23; mean change in Hospital Anxiety and Depression scale anxiety score: 1.6 with exercise *v* 0.9 with control, P = 0.2). It found an improvement in depressive symptoms in the exercise group compared with the control group (mean change in Hospital Anxiety and Depression scale depression score: 1.7 with exercise *v* 0.6 with control; P = 0.04). The additional RCT identified by the second systematic review (49 people with CFS, CDC criteria) compared graded exercise (increased activity to 30 minutes of exercise 5 times/week up to an energy expenditure of 70% of V_{O2} max) versus standard medical care over 12 weeks. [34] The RCT found that graded exercise significantly increased the proportion of people reporting they felt "much better" and "very much better" in a self-reported rating of improvement (7 possible responses ranged from "very much worse" to "very much better") compared with standard medical treatment (AR for "much better" or "very much better": 48% with graded exercise *v* 21% with standard medical care; P = 0.05).

Educational intervention including graded exercise versus control:
The review [33] identified one RCT (148 people with CFS, Oxford criteria). [38] The RCT compared three types of educational interventions with encouragement of graded exercise compared with written information only (control group). [38] People in the three educational-intervention groups received a minimum intervention consisting of two treatment sessions, two telephone follow-ups, and an educational package that provided an explanation of symptoms and encouraged home-based exercise. One group received the minimum intervention only; one group received seven additional follow-up telephone calls (telephone intervention); and another received seven additional face-to-face sessions over 4 months (maximum intervention). People in the written-information group received advice and an information booklet that encouraged graded activity, but gave no explanation for the symptoms. The RCT found no significant difference between the educational interventions. However, it found that the educational interventions significantly improved physical functioning (measured on the SF-36 physical function subscale; score range: 10–30, where 10 = maximum impairment and 30 = no impairment) and fatigue (measured on the Chalder fatigue scale; scale range: 0–11; a score greater than 3 indicates excessive fatigue) at 1 year compared with written information only (mean physical functioning score: 16.9 with control group *v* 25.1 with minimum intervention *v* 24.3 with telephone intervention *v* 24.9 with maximum intervention, P less than 0.001 for each intervention versus control; mean fatigue score: 10.6 with control group *v* 3.2 with minimum intervention *v* 3.5 with telephone intervention *v* 3.1 with maximum intervention, P less than 0.001 for each intervention versus control).

Harms:

None of the RCTs reported data on adverse effects, [34] [35] [36] [37] and we found no evidence that exercise is harmful in people with CFS. The second graded aerobic exercise RCT found no significant difference in withdrawal rates between graded exercise alone and no exercise, although withdrawal rates in both groups were high (25/68 [37%] with exercise *v* 15/69 [22%] without exercise; RR 1.70, 95% CI 0.98 to 2.90). [36] The reasons for the withdrawals from the graded-exercise groups were not reported.

Comment:

Clinical guide:
There is good evidence of benefit for graded exercise therapy in CFS. However, experience suggests that CFS symptoms may be exacerbated by overly ambitious or overly hasty attempts at exercise.

OPTION ANTIDEPRESSANTS

Overall improvement
Phenelzine compared with placebo Phenelzine may be more effective at improving symptoms of chronic fatigue syndrome (very low-quality evidence).

Moclobemide compared with placebo Moclobemide is no more effective at improving symptoms of chronic fatigue (high-quality evidence).

Sertaline compared with clomipramine Sertraline is no more effective at improving symptoms of chronic fatigue (moderate-quality evidence).

Fatigue
Fluoxetine compared with placebo Fluoxetine is no more effective at improving fatigue (moderate-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits:

We found one systematic review (search date 2005) [24] which did not conduct a meta-analysis or report quantified results from each study, and we found one additional RCT. [39]

Fluoxetine:
The systematic review [24] identified two RCTs. [40] [36] The first RCT (107 depressed and non-depressed people with chronic fatigue syndrome [CFS], Oxford criteria) compared fluoxetine versus placebo for 8 weeks. [40] It found that fluoxetine significantly improved the Beck Depression Inventory compared with placebo (mean difference between fluoxetine and placebo in improvement in Beck Depression Inventory: –0.19, 95% CI –0.35 to –0.02), but the difference was small, and possibly not clinically important. It found no significant difference between fluoxetine and placebo in fatigue severity (mean difference between fluoxetine and placebo on the fatigue subscale of Checklist Individual Strength: –0.16, 95% CI –0.64 to +0.31). [41] The second RCT (136 people with CFS, Oxford criteria) compared four groups: fluoxetine plus graded exercise; placebo plus graded exercise; fluoxetine plus general advice; and placebo plus general advice (see also graded exercise therapy, p 5). It found no significant difference between the groups using fluoxetine and the groups using placebo in the level of fatigue, although modest improvements in measures of depression were seen at 12 weeks in people using fluoxetine (Hospital Anxiety and Depression mean change 1.10, 95% CI 0.03 to 2.20). [36]

Phenelzine versus placebo:
The systematic review [24] identified one RCT. [42] The RCT (30 people with CFS, Centers for Disease Control and Prevention 1988 criteria) compared phenelzine versus placebo, using a modified Karnofsky scale and other outcome measures (including functional status questionnaire, profile of mood states, Centres for Epidemiological Study of Depression fatigue severity scale, and symptom severity checklist). [42] This RCT concluded that there was a pattern of improvement across several measures with phenelzine compared with placebo at 6 weeks (significance tests for individual measures not carried out).

Moclobemide versus placebo:
The systematic review [24] identified one RCT. [43] The RCT (90 people with CFS, Australian criteria, similar to Centres for Disease Control criteria) compared moclobemide 450–600 mg daily versus placebo. It found that, at 6 weeks, moclobemide was associated with a non-significant increase in self-reported global improvement (scale range from "improvement to non-improvement"; proportion reporting improvement: 24/47 [51%] with moclobemide *v* 14/43 [33%] with placebo; OR 2.16, 95% CI 0.90 to 5.10), and a non-significant improvement in the clinician-rated Karnofsky scale (standardised units of improvement: 0.86 with moclobemide *v* 0.58 with placebo; mean difference 0.28, 95% CI –0.2 to +0.8). [43]

Sertraline versus clomipramine:
We found one RCT (40 people with CFS), which found no significant difference in global improvement between sertraline and clomipramine (mean % improvement from baseline in the Clinical Global Impression scale: 31.8 with sertraline *v* 20.7 with clomipramine; P = 0.28). [39]

Other antidepressants:
We found no RCTs.

Harms:

Fluoxetine versus placebo:
The first RCT assessed the symptoms separately (which could be attributed to either chronic fatigue syndrome or to known adverse effects of fluoxetine) before starting treatment, after 2 weeks, after 6 weeks, and at the end of treatment (week 8). It found that fluoxetine significantly increased complaints of tremor and perspiration compared with placebo at 8 weeks (tremor: P = 0.006; perspiration: P = 0.008). [40] It found no significant difference between fluoxetine and placebo at 2 and 6 weeks. It found that fluoxetine was associated with increased withdrawal due to adverse effects compared with placebo (9/54 [17%] with fluoxetine *v* 2/53 [4%] with placebo; P value not reported). The second RCT also found increased withdrawal rates with fluoxetine (24/68 [36%] people with fluoxetine *v* 16/69 [24%] people with placebo; P value not reported). [36]

Phenelzine versus placebo:
Of 15 people who took phenelzine, three (20%) withdrew because of adverse effects, compared with none who took placebo. [42]

Moclobemide versus placebo:
The RCT reported that a total of 13/90 (14%) people withdrew from treatment owing to adverse effects: six from the placebo arm and seven from the moclobemide group. The adverse effects reported were agitation (5 people), headache (2 people), insomnia (6 people), gastrointestinal problems (5 people), malaise (4 people), and anxiety (3 people). However, the study did not report individual adverse effects according to treatment group. [43]

Sertraline versus clomipramine:
The RCT provided no information on adverse effects. [39]

Other antidepressants:
We found no RCTs.

Drug alert:
The FDA and other regulatory bodies have issued a number of alerts and revised prescribing information regarding the use of antidepressants — in particular relating to the increased risk of self-harm and suicide. [44] See reviews on depression in adults and depression in children and adolescents.

Comment:

Fluoxetine versus placebo:
The first RCT [40] used a shorter duration of treatment and studied people with a longer duration of illness compared with the second RCT. [36]

Clinical guide:
Although antidepressants have not been shown in RCTs to be of significant benefit, their use should be considered in people with depressive disorders. Tricyclic antidepressants have analgesic properties and may also be of benefit in people complaining of insomnia.

OPTION CORTICOSTEROIDS

Overall improvement
Fludrocortisone compared with placebo Fludrocortisone seems no more effective at improving symptoms of chronic fatigue (moderate-quality evidence).

Hydrocortisone compared with placebo Hydrocortisone may be more effective at improving overall symptoms of chronic fatigue (very low-quality evidence).

Fatigue
Hydrocortisone plus fludrocortisone compared with placebo Combined treatment with hydrocortisone plus fludrocortisone may be no more effective at improving fatigue (very low-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits:

We found one systematic review (search date 2005), [24] which did not conduct a meta-analysis or report quantified results from each study.

Fludrocortisone versus placebo:
The review [24] identified two RCTs. [45] [46] The first RCT (100 people with neurally mediated hypotension and chronic fatigue syndrome [CFS], Centers for Disease Control and Prevention [CDC] criteria) compared fludrocortisone (titrated to 0.1 mg/day) versus placebo for 9 weeks. [45] It found no significant difference on a self-rated 100-point global scale of "wellness" (AR for improvement of at least 15 points: 14% with fludrocortisone *v* 10% with placebo; P = 0.76; absolute figures not reported). [45] The second RCT (crossover design, 25 people, CDC criteria) measured change in symptom severity (visual analogue scale [VAS] of symptoms from 0–10 corresponding to "no problem" to "could not be worse") and functional status (using the SF-36) for 6 weeks. [46] It found no significant difference between fludrocortisone and placebo in symptom severity (change in fatigue score: 0.1 with fludrocortisone *v* 0.4 with placebo, P = 0.37; change in myalgia score: –0.3 with fludrocortisone *v* +1.1 with placebo, P = 0.53; change in concentration score: –0.9 with fludrocortisone *v* –0.3 with placebo, P = 0.4; change in joint pain score: –0.3 with fludrocortisone *v* 0.8 with placebo, P = 0.15) or functional status (change in physical functioning: +6.5 with fludrocortisone *v* –1.6 with placebo, P = 0.13; change in social functioning: 6.5 with fludrocortisone *v* 0.0 with placebo, P = 0.3).

Hydrocortisone versus placebo:
The review [24] identified two RCTs. [47] [48] The first RCT (65 people with CFS, CDC 1988 criteria) compared hydrocortisone 25–35 mg daily versus placebo for 12 weeks. [47] It found that hydrocortisone significantly improved "wellness" on a self-rated 100-point scale (AR for improvement of at least 5 points: 53% with hydrocortisone *v* 29% with placebo; P = 0.04). However, the clinical significance of this difference is unclear. Other self-rating scales did not show significant benefit with hydrocortisone (change in score from baseline: Beck Depression Inventory: –2.1 with hydrocortisone *v* –0.4 with placebo, P = 0.17; activity scale: 0.3 with hydrocortisone *v* 0.7 with placebo, P = 0.32; Sickness Impact Profile: –2.5 with hydrocortisone *v* –2.2 with placebo, P = 0.85). The second RCT (32 people with CFS, Oxford criteria, crossover design) compared a lower dose of hydrocortisone (5 or 10 mg daily) versus placebo for 1 month. [48] It found that hydrocortisone improved fatigue at 1 month compared with placebo (participant-assessed 11-item scale, overall score range 0–33, higher score indicates greater fatigue; mean pre-crossover score change from baseline: –6.7 with hydrocortisone *v* –2.4 with placebo; P value not reported, see comment below).

Hydrocortisone plus fludrocortisone versus placebo:
The review [24] identified one RCT (100 people with CFS, CDC criteria, crossover design, see comment below), which compared a combination of hydrocortisone 5 mg daily plus fludrocortisone 50 µg daily versus placebo for 3 months. [49] It found no significant difference in measures of subjective fatigue at 3 months (VAS from 0 = no fatigue to 10 = severe fatigue: mean score: 6.6 with corticosteroids *v* 6.7 with placebo, P = 0.76; Abbreviated Fatigue Questionnaire: mean score: 8 with corticosteroids *v* 7 with placebo, P = 0.69; pre-crossover results not presented, no washout period between treatments, see comment below).

Harms:

Fludrocortisone versus placebo:
In the first RCT, fludrocortisone increased withdrawal rates due to adverse events compared with placebo (12/50 [24%] with fludrocortisone *v* 4/50 [8%] with placebo; RR 3.00, 95% CI 1.04 to 8.67; NNH 6, 95% CI 3 to 8). [45] Three people receiving fludrocortisone withdrew from the second RCT because of worsening CFS symptoms (fatigue, headache, or insomnia). One person from the placebo group withdrew to have scheduled ovarian surgery. [46]

Hydrocortisone versus placebo:
The first RCT found that 12 people (40%) taking higher-dose hydrocortisone (25–35 mg daily) experienced adrenal suppression (assessed by measuring cortisol levels). [47] The second RCT reported minor adverse effects in up to 10% of people taking lower-dose hydrocortisone (5 or 10 mg daily). [48] Three people taking hydrocortisone had exacerbation of acne and nervousness, and one person taking placebo had an episode of fainting.

Hydrocortisone plus fludrocortisone versus placebo:
Two people withdrew from the RCT owing to concerns about the effect of corticosteroids, and one owing to adverse effects (acne and weight gain) of hydrocortisone plus fludrocortisone treatment. [49]

Comment:

The first RCT comparing fludrocortisone versus placebo determined *a priori* that an improvement of at least 5 points on a self-rated 100-point global scale of "wellness" was a meaningful change. [45] The results of the crossover RCTs should be interpreted with caution, as it is possible that treatment effects may persist after crossover. The RCTs used different reasons for their choice of active treatment. The use of fludrocortisone, a mineralocorticoid, was based on the hypothesis that CFS is associated with neurally mediated hypotension. [50] The use of hydrocortisone, a glucocorticoid, in the other RCTs was based on evidence of underactivity of the hypothalamic–pituitary–adrenocortical axis in some people with CFS. [51] The crossover RCT found that, although fatigue decreased with low-dose hydrocortisone, fatigue increased within 28 days of crossover into the placebo group. [48] Therefore, any benefit from low-dose hydrocortisone may be short lived, whereas higher doses are associated with adverse effects.

Clinical guide:
There is weak evidence of benefit for low-dose hydrocortisone; however, benefit may be short lived, and higher doses are associated with adverse effects.

OPTION DIETARY SUPPLEMENTS

Fatigue
Compared with placebo Dietary supplements may be no more effective at improving fatigue at 8–14 weeks (low-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table , p 19 .

Benefits:

Dietary supplements versus placebo:
We found one systematic review, (search date 2005) [24] which did not perform a meta-analysis or report quantified results from each study, and two subsequent RCTs. [52] [53] The systematic review identified one RCT comparing a polynutrient supplement (containing several vitamins, minerals, and coenzymes, taken twice daily) versus placebo for 10 weeks. [54] It found no significant difference in fatigue severity or functional impairment between treatments after 10 weeks (change in Checklist Individual Strength fatigue subscale [CIS-fatigue] from baseline to 10 weeks: 51.4 to 48.6 with supplements *v* 51.3 to 48.2 with placebo, difference +2.16, 95% CI –4.30 to +4.39; Sickness Impact Profile score less than 750 at 10 weeks: 4% with supplements *v* 12% with placebo, P value not reported). The first subsequent RCT (71 people with chronic fatigue syndrome [CFS], Centers for Disease Control and Prevention [CDC] criteria and two or more of: tender lymph nodes, sore throat, or poor temperature control) compared a food supplement (BioBran MGN-3) versus placebo for 8 weeks. [52] It found no significant difference between groups in fatigue severity (change in Chalder physical fatigue subscale from baseline to 8 weeks: –1.5 with BioBran *v* –1.8 with placebo; difference –0.3, 95% CI –3.2 to +2.6; P = 0.84). The second subsequent RCT (57 people

with CFS, CDC criteria) compared a food supplement (acclydine) versus placebo for 14 weeks. [53] The RCT found no significant difference in fatigue severity (CIS-fatigue) or functional impairment (Sickness Impact profile [SIP]-8) between acclydine and placebo (CIS-fatigue: difference +1.1, 95% CI –4.4 to +6.5, P = 0.70; SIP-8: difference +59.1, 95% CI –201.7 to +319.8, P = 0.65).

Harms: Three people (11%) on active treatment withdrew from the RCT identified by the systematic review because of nausea. [54] The first subsequent RCT reported that three people on active treatment withdrew because of mild nausea, an exacerbation of fatigue, or irritable bowel symptoms, and one person withdrew from the placebo group because of worsening fatigue (P value not provided). [52] The second subsequent RCT did not report on harms. [53]

Comment: **Clinical guide:**
We found insufficient evidence to recommend dietary supplements as a treatment in chronic fatigue syndrome.

OPTION EVENING PRIMROSE OIL

Physical function
Compared with placebo Evening primrose oil seems no more effective at improving physical function or other symptoms at 3 months (moderate-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits: **Evening primrose oil versus placebo:**
We found one systematic review (search date 2005) [24] which did not perform a meta-analysis or report quantified results from each study. The review identified one RCT (50 people with chronic fatigue syndrome [CFS], Oxford criteria), which compared evening primrose oil 4 g daily versus placebo for 3 months. [55] It found no significant difference between treatments in depression scores (measured using the Beck Depression Inventory), 15-point physical symptom score, or participant assessment at the end of treatment (change in depression score: –2.5 with evening primrose oil *v* –4.0 with placebo, P = 0.09; change in physical symptom score: –1.5 with evening primrose oil *v* –1.0 with placebo, P = 0.54; participant-reported improvement at 3 months: 29% with evening primrose oil *v* 46% with placebo, P = 0.09; RR and CI not reported).

Harms: The RCT reported no adverse effects. [55]

Comment: We found one RCT (63 people) comparing evening primrose oil 4 g daily versus placebo in people with a diagnosis of post-viral fatigue syndrome. [56] This diagnosis was made on the basis of overwhelming fatigue, myalgia, and depression, which had been present for at least 1 year, and preceded by a febrile illness. At 3 months, significantly more people on active treatment reported improvement compared with placebo (33/39 [85%] with evening primrose oil *v* 4/24 [17%]; P less than 0.0001). The difference in outcome may be partly explained by participant selection: the study in people with CFS used currently accepted diagnostic criteria. [55] Also, whereas the RCT in people with post-viral fatigue syndrome used liquid paraffin as a placebo, [56] the CFS RCT used sunflower oil, which is better tolerated and less likely to affect the placebo response adversely. [55]

Clinical guide:
There is insufficient evidence to recommend evening primrose oil as a treatment in CFS.

OPTION HOMEOPATHY

Overall improvement
Compared with placebo Homeopathy may be no more effective at improving overall symptoms of chronic fatigue (moderate-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits: **Homeopathy versus placebo:**
We found one systematic review (search date 2005) [24] which did not perform a meta-analysis or report quantified results from each study. The review identified one RCT, which compared homeopathic treatment (see comment) versus placebo for 6 months. [57] It found no significant difference in the proportion of participants considered to have clinically significant improvement (1 RCT, 103 people older than 18 years with chronic fatigue syndrome, Oxford criteria; AR for clinically significant improvement defined as at least 3 points improvement on the 5 Multidimensional Fatigue Inventory [MFI] subscales described below: 11/43 [26%] with homeopathy *v* 4/43 [9%] with placebo; P = 0.09). The study found that homeopathy significantly improved self-reported general fatigue after 6 months (mean change in MFI general fatigue subscale: 2.70 with homeopathy *v* 1.35 with placebo; P = 0.04).

However, there were no differences between homeopathy and placebo in self-reported physical fatigue, mental fatigue, activity, or motivation MFI subscales (mean changes in MFI physical fatigue subscale: 2.13 with homeopathy *v* 1.28 with placebo, P = 0.21; MFI mental fatigue subscale: 2.70 with homeopathy *v* 2.05 with placebo, P = 0.30; MFI reduced activity subscale: 2.72 with homeopathy *v* 1.81 with placebo, P = 0.16; MFI reduced motivation subscale: 1.35 with homeopathy *v* 1.65 with placebo, P = 0.82).

Harms: The RCT did not report data on adverse effects. [57]

Comment: As homeopathic prescribing methods are based on an assessment of the individual picture of illness, different homeopathic treatments were prescribed for different people within the RCT. [57] The analysis was reported by intention to treat; however, people who failed to provide outcome measures were excluded.

Clinical guide:
There is insufficient evidence to recommend homeopathy as a treatment in chronic fatigue syndrome.

OPTION MAGNESIUM (INTRAMUSCULAR)

Overall improvement
Compared with placebo Intramuscular magnesium injections may be more effective at improving symptoms at 6 months (moderate-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits: **Magnesium versus placebo:**
We found one systematic review (search date 2005), [24] which did not perform a meta-analysis or report quantified results from each study. The review identified one RCT (32 people with chronic fatigue syndrome [CFS], but not magnesium deficiency; Australian criteria; see comment below), which compared weekly intramuscular injections of magnesium sulphate 50% versus placebo injections (water) for 6 weeks. [58] It found that magnesium improved overall benefit (self-reported), Nottingham Health Profile energy, pain, and emotional reaction subscale scores compared with placebo (AR for reporting overall benefit: 12/15 [80%] with magnesium *v* 3/17 [18%] with placebo, RR 4.5, 95% CI 1.6 to 13.1, NNT 2, 95% CI 2 to 4; Nottingham Health Profile mean change in score from baseline for magnesium *v* placebo: energy subscale –51.04 with magnesium *v* –4.5 with placebo, P = 0.002; pain subscale –19.63 with magnesium *v* +2.7 with placebo, P = 0.001; emotional reaction subscale –33.3 with magnesium *v* +7.4 with placebo, P = 0.013; score decrease represents improvement).

Harms: The RCT reported no adverse effects. [58]

Comment: In the RCT, plasma and whole blood magnesium were normal, and only the red blood cell concentrations of magnesium were slightly lower than the normal range. [58] Three subsequent case control studies have not found a deficiency of magnesium in people with CFS. [59] [60] [61] In these three studies, magnesium was in the normal range and no different from controls without CFS. However, none of the studies state how the normal range was established, so it is difficult to say whether they are equivalent.

Clinical guide:
There is no good evidence that intramuscular magnesium is of benefit in CFS.

OPTION NICOTINAMIDE ADENINE DINUCLEOTIDE (ORAL)

Overall improvement
Compared with placebo Oral nicotinamide adenine dinucleotide may be more effective at improving symptoms in people with chronic fatigue syndrome at 4 weeks (very low-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits: **Oral nicotinamide adenine dinucleotide versus placebo:**
We found one systematic review (search date 2005), [24] which did not perform a meta-analysis or report quantified results from each study. It identified one poor-quality randomised crossover trial (35 people with chronic fatigue syndrome, Centers for Disease Control and Prevention criteria), which compared nicotinamide adenine dinucleotide 10 mg daily versus placebo for 4 weeks. [62] Of the 35 people, two were excluded from the analysis for non-compliance, and seven were excluded for using psychotropic drugs. The RCT found that nicotinamide adenine dinucleotide significantly improved symptom scores compared with placebo (measured on a self-devised 50-item symptom

rating scale; AR for 10% improvement: 8/26 [30%] people with nicotinamide adenine dinucleotide *v* 2/26 [8%] people with placebo; P less than 0.05; analysis not by intention to treat; see comment below).

Harms: Minor adverse effects (loss of appetite, dyspepsia, and flatulence) were reported with active treatment, but no one stopped treatment as a result. [62]

Comment: The RCT determined *a priori* that a 10% improvement in symptom scores was a meaningful improvement. [62] The RCT had several problems with its methods, including the use of inappropriate statistical analyses, the inappropriate exclusion of people from the analysis, and lack of numerical data preventing independent analysis of the published results. [63]

Clinical guide:
There is no good evidence that oral nicotinamide adenine dinucleotide is of benefit in chronic fatigue syndrome compared with placebo.

OPTION PROLONGED REST

We found no clinically important results about the effects of prolonged rest in people with chronic fatigue syndrome.

For GRADE evaluation of interventions for chronic fatigue syndrome, **see table, p 19** **.**

Benefits: We found no systematic review or RCTs of prolonged rest in people with chronic fatigue syndrome.

Harms: We found no direct evidence of harmful effects of rest in people with chronic fatigue syndrome. We found observational evidence, which suggested that prolonged inactivity may perpetuate or worsen fatigue, and is associated with symptoms in both healthy volunteers [64] and people recovering from viral illness. [65] [66]

Comment: It is not clear that evidence from people recovering from viral illness or in healthy volunteers can be extrapolated to people with chronic fatigue syndrome.

Clinical guide:
Although we found no RCTs of prolonged rest in people with chronic fatigue syndrome, historically it has been recommended as a treatment. However, indirect evidence suggests that prolonged rest may be ineffective and potentially harmful.

OPTION GALANTAMINE

Overall improvement
Compared with placebo Galantamine does not seem to increase symptomatic improvement at 16 weeks compared with placebo (moderate-quality evidence).

For GRADE evaluation of interventions for chronic fatigue syndrome, **see table, p 19** **.**

Benefits: **Galantamine versus placebo:**
We found one systematic review (search date 2005), [24] which did not perform a meta-analysis or report quantified results from each study. The review identified one RCT (434 people, aged between 18–65 years, with chronic fatigue syndrome, Centers for Disease Control and Prevention criteria; illness duration less than 7 years) which compared four different dosages of galantamine hydrobromide (7.5 mg, 15 mg, 22.5 mg, or 30 mg daily) versus placebo. [67] The RCT found no significant difference in the proportion of people reporting symptomatic improvement (defined as a rating of "much improved" and "very much improved" on the Clinical Global Impression scale) at 16 weeks (AR for symptomatic improvement: 29% with 7.5 mg galantamine *v* 23% with 15 mg galantamine *v* 22% with 22.5 mg galantamine *v* 20% with 30 mg galantamine *v* 18% with placebo; difference in response rate between galantamine and placebo: 11% with 7.5 mg; 5% with 15 mg; 4% with 22.5 mg; 2% with 30 mg; reported as not significant; P value not reported). The difference between each galantamine dose and placebo in the proportion of people with symptomatic improvement was less than the prespecified level for clinical significance of 25%.

Harms: **Galantamine versus placebo:**
The RCT reported that 88 people withdrew owing to adverse effects, notably nausea, headache, and depression. [67] The number of people withdrawing increased with higher doses of galantamine; but there were no statistically significant differences between groups (12/89 [13%] with 7.5 mg galantamine *v* 20/86 [23%] with 15 mg galantamine *v* 22/91 [24%] with 22.5 mg galantamine *v*

22/86 [26%] with 30 mg galantamine *v* 12/82 [15%] with placebo; differences reported as not significant; P values not reported).

Comment: The RCT had a high withdrawal rate (20%); however, its analyses included 97% (423/434) of participants using the last observation carried forward method. [67]

Clinical guide:
The evidence suggests that galantamine provides no meaningful benefit in people with chronic fatigue syndrome.

OPTION IMMUNOTHERAPY

Overall improvement
Immunoglobulin G compared with placebo We don't know whether immunoglobulin G is more effective at improving overall symptoms of chronic fatigue (low-quality evidence).

Dialysable leucocyte extract compared with placebo Dialysable leucocyte extract may be no more effective at improving symptoms of chronic fatigue (very low-quality evidence).

Staphylococcus toxoid compared with placebo Staphylococcus toxoid may be more effective at improving overall symptoms (low-quality evidence).

Fatigue
Immunoglobulin G compared with placebo Immunoglobulin G may be no more effective at improving chronic fatigue (low-quality evidence).

Adverse effects
Immunoglobulin G is associated with considerable adverse effects, such as headache. Staphylococcus toxoid is associated with local reactions and can cause anaphylaxis.

Note
We found no clinically important results about the effects of interferon alfa or aciclovir compared with placebo.

For GRADE evaluation of interventions for chronic fatigue syndrome, see table, p 19 .

Benefits: We found one systematic review (search date 2005), [24] which did not perform a meta-analysis or report quantified results from each study.

Immunoglobulin G versus placebo:
The review identified four RCTs comparing immunoglobulin G versus placebo for 6 months. [68] [69] [70] [71] The first RCT (30 people with chronic fatigue syndrome [CFS], Centers for Disease Control and Prevention [CDC] 1988 criteria) compared monthly intravenous injections of immunoglobulin G 1 g/kg versus placebo (albumin). [68] The RCT found no significant difference after 6 months in measures of fatigue (percentage improvement in self-reported symptom severity: 0.0 with immunoglobulin G *v* 14.3 with placebo; reported as non-significant; P value not reported) or in physical functioning (mean change in SF-36 physical functioning subscale: –7.1 with immunoglobulin G *v* –14.3 with placebo; reported as non-significant; P value not reported). It found that placebo significantly improved social function compared with immunoglobulin G (dichotomous figures and P value not reported). The second RCT (49 people with CFS, Australian criteria, similar to CDC criteria) compared monthly intravenous immunoglobulin G 2 g/kg versus intravenous placebo (a maltose solution) for 3 months. [69] It found that immunoglobulin G significantly increased the proportion of people with physician-rated improvement in symptoms and disability 3 months after the completion of treatment compared with placebo (10/23 [44%] with immunoglobulin G *v* 3/26 [12%] with placebo; P = 0.03). The third RCT (99 adults with CFS, Australian criteria) compared low, medium, and high doses of immunoglobulin G (0.5, 1, or 2 g/kg) versus placebo (albumin). [70] It found no significant difference between groups at 6 months in improvement in Karnofsky performance score or quality-of-life scores on visual analogue scales (improvement in median Karnofsky score: 2.5 with low dose *v* 10 with medium dose *v* 5 with high dose *v* 7.5 with placebo, P greater than 0.13; quality of life: P greater than 0.09, scores not reported). The fourth RCT (71 adolescents aged 11–18 years with CFS, CDC criteria) compared immunoglobulin G 1 g/kg versus placebo (a solution of maltose plus albumin). [71] Three infusions were given 1 month apart. The RCT found that immunoglobulin G significantly improved mean functional outcome (assessed using the mean of clinician ratings from 4 areas of the participants' activities) at 6 months compared with placebo (AR for improvement of at least 25%: 26/36 [72%] with immunoglobulin G *v* 15/34 [44%] with placebo; P less than 0.02).

Interferon alfa versus placebo:
The review identified two RCTs. [72] [73] The first RCT (30 people with CFS, Oxford criteria, crossover design) identified by the review only found treatment benefit on subgroup analysis of people with diminished natural killer cell function but normal lymphocyte proliferation. [72] The second RCT (20 people with CFS, crossover design) identified by the review did not present results in a manner that allowed clear interpretation of treatment effect. [73]

Staphylococcus toxoid versus placebo:
One RCT (100 women who met both the American Cancer Society criteria for fibromyalgia and the CDC criteria for CFS and had functional impairment lasting more than 6 months) identified by the review compared weekly subcutaneous injections of staphylococcus toxoid (dose increased weekly from 0.1 mL to 1.0 mL, followed by 1.0 mL doses every 4 weeks) versus placebo. [74] It found that staphylococcus toxoid significantly improved the Clinical Global Impression scale at 26 weeks compared with placebo (AR for "minimally improved", "much improved", or "very much improved": 32/49 [65%] with toxoid *v* 9/49 [18%] with placebo; P less than 0.001).

Aciclovir versus placebo:
One RCT in the review found no significant difference between aciclovir and placebo. [75]

Dialysable leucocyte extract versus placebo or CBT:
See benefits of CBT, p 3 . [26]

Harms:

Immunoglobulin G:
In the first RCT, adverse effects judged to be worse than symptoms before treatment in either group included gastrointestinal complaints (18 people), headaches (23 people), myalgia or arthralgia (6 people), and fever (10 people). [68] Of these symptoms, only headaches differed significantly between the groups (14/15 [93%] with immunoglobulin G *v* 9/15 [60%] with placebo; P = 0.03). Three people in each group had major adverse effects, and one person in each group withdrew from the trial as a consequence. The RCT only reported adverse events by treatment group for headache. In the second RCT, phlebitis, headache, and worsening fatigue occurred more frequently with immunoglobulin G compared with placebo (phlebitis: 35/65 [54%] with immunoglobulin G *v* 1/78 [1%] with placebo, P less than 0.001; headache and worsening fatigue: 53/65 [82%] with immunoglobulin G *v* 19/78 [24%] with placebo, P less than 0.001). [69] The third RCT found no significant difference between immunoglobulin G (0.5, 1, or 2 g/kg) and placebo in the occurrence of headaches, worsened fatigue, malaise, and concentration impairment (18/22 [82%] with 0.5 g/kg immunoglobulin G *v* 20/28 [71%] with 1 g/kg immunoglobulin G *v* 18/23 [78%] with 2 g/kg immunoglobulin G *v* 23/26 [88%] with placebo; P = 0.49). [70] In the fourth RCT, severe headaches occurred in 64% of the immunoglobulin G group after the first infusion, compared with 20% of those receiving placebo (P less than 0.01). [71]

Interferon alfa versus placebo:
In one RCT comparing interferon alfa versus placebo, 2/13 (15%) people taking active treatment developed neutropenia. [72]

Staphylococcus toxoid versus placebo:
The RCT comparing staphylococcus toxoid versus placebo found no significant difference between groups in reported adverse effects, excluding local reactions (13/49 [26%] with toxoid *v* 7/49 [14%] with placebo; P = 0.14). [74] All those receiving the toxoid had a local reaction at the injection site.

Comment:

Immunoglobulin G:
The first two RCTs differed in that the second used twice the dose of immunoglobulin G, did not require participants to fulfil the operational criteria (similar but not identical to the CDC criteria) for CFS, and made no assessments of them during the study, instead waiting until 3 months after completion. [69]

Clinical guide:
Given the weak evidence of benefit for immunotherapy, the potential harms indicate that it should not be offered as a treatment for CFS.

GLOSSARY

Beck Depression Inventory Standardised scale to assess depression. This instrument consists of 21 items to assess the intensity of depression. Each item is a list of four statements (rated 0, 1, 2, or 3), arranged in increasing severity, about a particular symptom of depression. The range of scores possible are 0 = least severe depression to 63 = most severe depression. It is recommended for people aged 13–80 years. Scores of more than 12 or 13 indicate the presence of depression.

Cognitive behavioural therapy Brief (6–20 sessions over 12–16 weeks) structured treatment, incorporating elements of cognitive therapy and behavioural therapy. Behavioural therapy is based on learning theory and concentrates on changing behaviour. It requires a highly trained therapist.
Chronic fatigue syndrome, Australian definition (1) Chronic persisting or relapsing fatigue of a generalised nature, exacerbated by minor exercise, causing significant disruption of usual daily activities, and present for more than 6 months; (2) Neuropsychiatric dysfunction including impairment of concentration evidenced by difficulty in completing mental tasks that were easily accomplished before the onset of the syndrome; new onset of short-term memory impairment; (3) No alternative diagnosis reached by history, physical examination, or investigations over a 6-month period. [3]
Clinical Global Impression Scale is a one-item, observer-rated scale for measuring the severity of a condition. It has been investigated for validity and reliability. It is scored on a scale from 0 (not ill at all) to 7 (severely ill).
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

CBT One RCT added comparing three interventions: group CBT, usual care, and education and support (including relaxation), [25] which found that CBT improved the SF-36 mental health score, and Hospital Anxiety and Depression score (HADS) in anxiety, compared with usual care and decreased physical fatigue compared with both usual care and education and support; benefits data enhanced; categorisation unchanged (beneficial).
Dietary supplements One RCT added [53] which found no significant difference between acclydine and placebo in fatigue severity or functional impairment; benefits data enhanced; categorisation unchanged (Unknown effectiveness).

REFERENCES

1. Fukuda K, Straus S, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;121:953–959.[PubMed]
2. Sharpe M, Archard LC, Banatvala JE. A report – chronic fatigue syndrome: guidelines for research. *J R Soc Med* 1991;84:118–121. [PubMed]
3. Lloyd AR, Hickie I, Boughton DR, et al. Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust* 1990;153:522–528.[PubMed]
4. Reeves WC, Lloyd A, Vernon S D, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Services Research* 2003;3:25. Available online at: http://www.biomedcentral.com/1472-6963/3/25 (last accessed 24 July 2008).
5. Afari N, Buchwald D. Chronic fatigue syndrome: a review. *Am J Psychiatry* 2003;160:221–236.[PubMed]
6. White P, Thomas J, Kangro H, et al. Predictions and associations of fatigue syndromes and mood disorders that occur after infectious mononucleosis. *Lancet* 2001;358:1946–1954.[PubMed]
7. Harvey SB, Wadsworth M, Wessely S, et al. The relationship between prior psychiatric disorder and chronic fatigue: evidence from a national birth cohort study. *Psychol Med* 2008;38:933–940.[PubMed]
8. Steele L, Dobbins JG, Fukuda K, et al. The epidemiology of chronic fatigue in San Francisco. *Am J Med* 1998;105(suppl 3A):83–90.
9. Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. *Arch Intern Med* 1999;159:2129–2137.[PubMed]
10. Wessely S. The epidemiology of chronic fatigue syndrome. *Epidemiol Rev* 1995;17:139–151.[PubMed]
11. Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. *QJM* 1997;90:223–233. Search date 1996; primary sources Medline, Embase, Current Contents, and Psychlit.[PubMed]
12. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. *Occup Med (Oxford)* 2005;55:20–31.[PubMed]
13. Stewart AD, Hays RD, Ware JE. The MOS short-form general health survey. *Med Care* 1988;26:724–732.[PubMed]
14. Karnofsky DA, Burchenal JH, MacLeod CM. *The clinical evaluation of chemotherapeutic agents in cancer.* New York: Columbia University Press, 1949:191–206.
15. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–571.[PubMed]
16. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale (HAD). *Acta Psychiatr Scand* 1983;67:361–370.[PubMed]
17. Bergner M, Bobbit RA, Carter WB, et al. The sickness impact profile: development and final revision of a health status measure. *Med Care* 1981;19:787–805.[PubMed]
18. Chalder T, Berelowitz C, Pawlikowska T. Development of a fatigue scale. *J Psychosom Res* 1993;37:147–154.[PubMed]
19. Alberts M, Smets EM, Vercoulen JH, et al. Abbreviated fatigue questionnaire: a practical tool in the classification of fatigue [In Dutch]. *Ned Tijdschr Geneeskd* 1997;141:1526–1530. [PubMed]
20. Guy W. *ECDEU assessment manual for psychopharmacology*. Rockville: National Institute of Mental Health, 1976:218–222.
21. Vercoulen JH, Swanink CM, Fennis JF, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38:383–392.[PubMed]
22. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Prac* 1985,35:185–188.
23. Smets EMA, Garrson B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39:315–325.[PubMed]
24. Chambers D, Bagnall A-M, Hempel S, et al. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: An updated systematic review. *J Royal Soc Med* 2006;99:506–520.[PubMed]
25. O'Dowd H, Gladwell P, Rogers CA, et al. Cognitive behavioural therapy in chronic fatigue syndrome: A randomised controlled trial of an outpatient group programme. *Health Technol Assess* 2006;10:iii-iv, ix-x, 1-121.[PubMed]
26. Lloyd A, Hickie I, Boughton R, et al. Immunologic and psychological therapy for patients with chronic fatigue syndrome. *Am J Med* 1993;94:197–203.[PubMed]
27. Sharpe M, Hawton K, Simkin S, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a randomized controlled trial. *BMJ* 1996;312:22–26.[PubMed]
28. Deale A, Chalder T, Marks I, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry* 1997;154:408–414.[PubMed]
29. Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet* 2001;357:841–847.[PubMed]
30. Stulemeijer M, de Jong LWAM, Fiselier TJW, et al. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ* 2005;330:14.[PubMed]
31. Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behaviour therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry* 2001;158:2038–2042.[PubMed]
32. Ridsdale L, Godfrey E, Chalder T, et al. Chronic fatigue in general practice: is counselling as good as cognitive behaviour therapy? A UK randomised trial. *Br J Gen Pract* 2001;51:19–24.[PubMed]
33. Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. In: The Cochrane Library: Issue 3, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004.
34. Moss-Morris R, Sharon C, Tobin R, et al. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol* 2005;10:245–259.[PubMed]
35. Fulcher KY, White PD. A randomised controlled trial of graded exercise therapy in patients with the chronic fatigue syndrome. *BMJ* 1997;314:1647–1652.[PubMed]
36. Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo controlled treatment trial of fluoxetine and a graded exercise programme for chronic fatigue syndrome. *Br J Psychiatry* 1998;172:485–490.[PubMed]
37. Wallman KE, Morton AR, Goodman C, et al. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust* 2004;180:444–448.[PubMed]
38. Powell P, Bentall RP, Nye FJ, et al. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ* 2001;322:387–390.[PubMed]
39. Behan PO, Hannifah H. 5-HT reuptake inhibitors in CFS. *J Immunol Immunopharmacol* 1995;15:66–69.
40. Vercoulen J, Swanink C, Zitman F. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet* 1996;347:858–861.[PubMed]
41. Vercoulen JHMM, Swanink CMA, Galama JMD, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38:383–392.[PubMed]

42. Natelson BH, Cheu J, Pareja J, et al. Randomised, double blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndrome. *Psychopharmacology* 1996;124:226–230.[PubMed]
43. Hickie IB, Wilson AJ, Murray Wright J, et al. A randomized, double-blind, placebo-controlled trial of moclobemide in patients with chronic fatigue syndrome. *J Clin Psychiatry* 2000;61:643–648.[PubMed]
44. MedWatch website. http://www.fda.gov/medwatch/
45. Rowe PC, Calkins H, DeBusk K, et al. Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome. *JAMA* 2001;285:52–59.[PubMed]
46. Peterson PK, Pheley A, Schroeppel J, et al. A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome. *Arch Intern Med* 1998;158:908–914.[PubMed]
47. McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome. *JAMA* 1998;280:1061–1066.[PubMed]
48. Cleare AJ, Heap E, Malhi G, et al. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. *Lancet* 1999;353:455–458.[PubMed]
49. Blockmans D, Persoons P, Van Houdenhove B, et al. Combination therapy with hydrocortisone and fludrocortisone does not improve symptoms in chronic fatigue syndrome: a randomized, placebo-controlled, double-blind, crossover study. *Am J Med* 2003;114:736–741.[PubMed]
50. Bou-Holaigah I, Rowe P, Kan J, et al. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 1995;274:961–967.[PubMed]
51. Demitrack M, Dale J, Straus S, et al. Evidence for impaired activation of the hypothalamic pituitary adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab* 1991;73:1224–1234.[PubMed]
52. McDermott C, Richards SCM, Thomas PW, et al. A placebo-controlled, double-blind, randomized controlled trial of a natural killer cell stimulant (BioBran MGN-3) in chronic fatigue syndrome. *Q J Med* 2006;99:461–468.[PubMed]
53. The GKH, Bleijenberg G, Van der Meer JW. The effect of acclydine in chronic fatigue syndrome: A randomized controlled trial. *PLoS ClinTrials* 2007;2.[PubMed]
54. Brouwers FM, van der Werf S, Bleijenberg G, et al. The effect of a polynutrient supplement on fatigue and physical activity of patients with chronic fatigue syndrome: a double-blind randomized controlled trial. *QJM* 2002;95:677–683.[PubMed]
55. Warren G, McKendrick M, Peet M. The role of essential fatty acids in chronic fatigue syndrome. *Acta Neurol Scand* 1999;99:112–116.[PubMed]
56. Behan PO, Behan WMH, Horrobin D. Effect of high doses of essential fatty acids on the postviral fatigue syndrome. *Acta Neurol Scand* 1990;82:209–216.[PubMed]
57. Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. *J Psychosom Res* 2004;56:189–197.[PubMed]
58. Cox IM, Campbell MJ, Dowson D. Red blood cell magnesium and chronic fatigue syndrome. *Lancet* 1991;337:757–760[PubMed]
59. Clague JE, Edwards RHT, Jackson MJ. Intravenous magnesium loading in chronic fatigue syndrome. *Lancet* 1992;340:124–125.[PubMed]
60. Hinds G, Bell NP, McMaster D, et al. Normal red cell magnesium concentrations and magnesium loading tests in patients with chronic fatigue syndrome. *Ann Clin Biochem* 1994;31:459–461.[PubMed]
61. Swanink CM, Vercoulen JH, Bleijenberg G, et al. Chronic fatigue syndrome: a clinical and laboratory study with a well matched control group. *J Intern Med* 1995;237:499–506[PubMed]
62. Forsyth LM, Preuss HG, MacDowell AL, et al. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1999;82:185–191.[PubMed]
63. Colquhoun D, Senn S. Re: therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 2000;84:639–640.[PubMed]
64. Sandler H, Vernikos J. *Inactivity: physiological effects.* London: Academic Press, 1986.
65. Dalrymple W. Infectious mononucleosis: 2. Relation of bed rest and activity to prognosis. *Postgrad Med* 1961;35:345–349.
66. Candy B, Chalder T, Cleare AJ, et al. Recovery from infectious mononucleosis: a case for more than symptomatic therapy? A systematic review. *Br J Gen Pract* 2002; 52:844–851.
67. Blacker CVR, Greenwood DT, Wesnes KA, et al. Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized controlled trial. *JAMA* 2004;292:1195–1204.[PubMed]
68. Peterson PK, Shepard J, Macres M, et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. *Am J Med* 1990;89:554–560.[PubMed]
69. Lloyd A, Hickie I, Wakefield D, et al. A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. *Am J Med* 1990;89:561–568.[PubMed]
70. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med* 1997;103:38–43.[PubMed]
71. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. *J Psychiatr Res* 1997;31:133–147.[PubMed]
72. See DM, Tilles JG. Alpha interferon treatment of patients with chronic fatigue syndrome. *Immunol Invest* 1996;25:153–164.[PubMed]
73. Brook M, Bannister B, Weir W. Interferon-alpha therapy for patients with chronic fatigue syndrome. *J Infect Dis* 1993;168:791–792.[PubMed]
74. Zachrisson O, Regland B, Jahreskog M, et al. Treatment with staphylococcus toxoid in fibromyalgia/chronic fatigue syndrome – a randomised controlled trial. *Eur J Pain* 2002;6:455–466.[PubMed]
75. Straus SE, Dale JK, Tobi M, et al. Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo-controlled trial. *N Engl J Med* 1988;319:1692–1698.[PubMed]

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Disclaimer

TABLE 1 **Diagnostic criteria for chronic fatigue syndrome (see text).**

CDC 1994 [1]	Oxford, UK [2]
Clinically evaluated, medically unexplained fatigue of at least 6 months' duration that is:	Severe, disabling fatigue of at least 6 months' duration that:
– of new onset	– affects both physical and mental functioning
– not a result of ongoing exertion	– was present for more than 50% of the time
– not substantially alleviated by rest	
– a substantial reduction in previous levels of activity	
The occurrence of four or more of the following symptoms:	Other symptoms, particularly myalgia, sleep and mood disturbance, may be present.
– subjective memory impairment	
– tender lymph nodes	
– muscle pain	
– joint pain	
– headache	
– unrefreshing sleep	
– postexertional malaise (greater than 24 hours)	
Exclusion criteria	
– active, unresolved, or suspected disease likely to cause fatigue	– active, unresolved, or suspected disease likely to cause fatigue
– psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)	– psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)
– psychotic disorders	– psychotic disorders
– dementia	– dementia
– anorexia or bulimia nervosa	– anorexia or bulimia nervosa
– alcohol or other substance misuse	
– severe obesity	

CDC, US Centers for Disease Control and Prevention

TABLE **GRADE evaluation of interventions for chronic fatigue syndrome**

Important outcomes			Symptom severity, adverse effects						
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for chronic fatigue syndrome?									
1 (60) [28]	Overall Improvement	CBT *v* control interventions	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (303) [26] [27] [25]	Quality of life	CBT *v* control interventions	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results, and inclusion of multiple comparisons with no statistical adjustments. Consistency point deducted for conflicting results
3 (500) [30] [29] [25]	Fatigue	CBT *v* control interventions	4	–3	0	0	0	Very low	Quality points deducted for poor follow-up, flaws in analysis, and incomplete reporting of results
2 (213) [25] [28]	Physical functioning	CBT *v* control interventions	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, and inclusion of multiple comparisons with no stastistical adjustment
3 (176) [34] [35] [37]	Overall improvement	Graded exercise therapy *v* control interventions	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
2 (197) [36] [37]	Fatigue/physical function	Graded exercise therapy *v* control interventions	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
1 (148) [38]	Fatigue/physical functioning	Graded exercise therapy education *v* written information	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (243) [16] [36] [40] [41]	Fatigue	Fluoxetine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for heterogeneity in studies
1 (30) [42]	Overall improvement	Phenelzine *v* placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
1 (90) [43]	Overall improvement	Moclobemide *v* placebo	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for OR greater than 2
1 (40) [39]	Overall improvement	Sertraline *v* clomipramine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (125) [45] [46]	Overall improvement	Fludrocortisone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (97) [47] [48]	Overall improvement	Hydrocortisone *v* placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
1 (100) [49]	Fatigue	Hydrocortisone plus fludrocortisone *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, methodological flaws, and incomplete reporting of results
3 (at least 128) [54] [53]	Fatigue	Dietary supplements *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (50) [55]	Physical function	Evening primrose oil *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (103) [57]	Overall improvement	Homeopathy *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes			Symptom severity, adverse effects						
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (32) [58]	Overall improvement	Magnesium injections *v* placebo	4	–2	0	0	1	Moderate	Quality point deducted for sparse data and methodological flaws. Effect-size point added for RR greater than 4
1 (35) [62]	Overall improvement	Oral nicotinamide adenine dinucleotide *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
1 (434) [67]	Overall improvement	Galantamine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (219) [67] [70] [71]	Overall improvement	Immunoglobulin G *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for different diagnostic criteria
1 (30) [68]	Fatigue/physical function	Immunoglobulin *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (90) [26]	Overall improvement	Dialysable leucocyte extract *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deleted for inclusion of multiple comparisons
1 (100) [74]	Overall improvement	Staphylococcus toxoid *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes.